PATENT COOPERATION TREATY

FILE COPY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MA 02110-2214

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*)
Applicant's or agent's file reference 50082/015WO2	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US01/32136	International filing date (*day/month/year*) 11 October 2001 (11.10.2001)
Applicant VIRION THERAPEUTICS INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompany sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application , or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D. Telephone No. 703-308-0196

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MA 02110-2214

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Applicant's or agent's file reference 50082/015WO2	Date of Mailing *(day/month/year)*
International application No. PCT/US01/32136	**PAYMENT DUE** within 15 days from the above date of mailing
Applicant VIRION THERAPEUTICS INC.	International filing date *(day/month/year)* 11 October 2001 (11.10.2001)

1. This International Searching Authority

(i) considers that there are 33 *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
Please See Continuation Sheet

and it considers that **the international application does not comply with the requirements of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
Please See Continuation Sheet

(ii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.: 1-10, 42 and 43 as they read on SEQ ID NO:1.

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

$210.00	X	32	=	$6,720.00
Fee additional per invention		number of additional inventions		total amount of additional fees

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☐ Claim(s) Nos. ____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D. Telephone No. 703-308-0196

Form PCT/ISA/206 (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US01/32136

This International Search Authority has found 33 inventions claimed in the International Application covered by the claims indicated below:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-10, 42 and 43 drawn to a polypeptide of a *Yatapoxvirus* and a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 1, a Tanapox virus protein sequence.

Group 2, claim(s) 1-10, 42 and 43 drawn to a polypeptide of a *Yatapoxvirus* and a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 2, a Yaba Monkey Tumor Virus protein sequence.

Group 3, claim(s) 1-10, 42 and 43 drawn to a polypeptide of a *Yatapoxvirus* and a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 4, a Tanapox virus protein sequence.

Group 4, claim(s) 1-10, 42 and 43 drawn to a polypeptide of a *Yatapoxvirus* and a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 6, a Yaba-like disease virus protein sequence.

Group 5, claim(s) 1-10, 42 and 43 drawn to a polypeptide of a *Yatapoxvirus* and a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 8, a Swinepox virus protein sequence.

Group 6, claim(s) 11-26, 32, 33 and 47, drawn to the nucleic acid encoding a *Yatapoxvirus* protein, the nucleotide sequence comprises SEQ ID NO: 3.

Group 7, claim(s) 11-26, 32, 33 and 47, drawn to the nucleic acid encoding a *Yatapoxvirus* protein, the nucleotide sequence comprises SEQ ID NO: 5.

Group 8, claim(s) 11-26, 32, 33 and 47, drawn to the nucleic acid encoding a *Yatapoxvirus* protein, the nucleotide sequence comprises SEQ ID NO: 7.

Group 9, claim(s) 27-29, drawn to a transgenic animal comprising a *Yatapoxvirus* gene.

Group 10, claim(s) 30, 31 and 48, drawn to an antibody to a *Yatapoxvirus* protein. Selection of one of the following species SEQ ID NO: 1, a Tanapox virus protein sequence.

Group 11, claim(s) 30, 31 and 48, drawn to an antibody to a *Yatapoxvirus* protein. Selection of one of the following species SEQ ID NO: 2, a Yaba Monkey Tumor Virus protein sequence.

Group 12, claim(s) 30, 31 and 48, drawn to an antibody to a *Yatapoxvirus* protein. Selection of one of the following species SEQ ID NO: 4, a Tanapox virus protein sequence.

Group 13, claim(s) 30, 31 and 48, drawn to an antibody to a *Yatapoxvirus* protein. Selection of one of the following species SEQ ID NO: 6, a Yaba-like disease virus protein sequence.

Group 14, claim(s) 34, drawn to a method of detecting a polypeptide of a *Yatapoxvirus*.

Group 15, claim(s) 35, drawn to a method of detecting a gene of a *Yatapoxvirus* comprising SEQ ID NO: 3.

Group 16, claim(s) 35, drawn to a method of detecting a gene of a *Yatapoxvirus* comprising species SEQ ID NO: 5.

Group 17, claim(s) 35, drawn to a method of detecting a gene of a *Yatapoxvirus* comprising SEQ ID NO: 7.

Group 18, claim(s) 36, drawn to a method of identifying an immunomodulator gene of a *Yatapoxvirus*.

Group 19, claim(s) 37 and 43, drawn to identifying a test compound that modulates the expression of a *Yatapoxvirus* gene comprising a substantially identical sequence to SEQ ID NO: 1.

Group 20, claim(s) 37 and 43, drawn to identifying a test compound that modulates the expression of a *Yatapoxvirus* gene comprising a substantially identical sequence to SEQ ID NO: 2.

Group 21, claim(s) 37 and 43, drawn to identifying a test compound that modulates the expression of a *Yatapoxvirus* gene comprising a substantially identical sequence to SEQ ID NO: 4.

Group 22, claim(s) 37 and 43, drawn to identifying a test compound that modulates the expression of a *Yatapoxvirus* gene comprising a substantially identical sequence to SEQ ID NO: 6.

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US01/32136

Group 23, claim(s) 49 and 55, drawn to identifying a test compound that modulates the expression of a *Yatapoxvirus* gene comprising a substantially identical sequence to SEQ ID NO: 8.

Group 24, claim(s) 38 and 43, drawn to a method of targeting protein for secretion from a cell, the protein comprising a sequence substantially identical to SEQ ID NO: 1.

Group 25, claim(s) 38 and 43, drawn to a method of targeting protein for secretion from a cell, the protein comprising a sequence substantially identical to SEQ ID NO: 2.

Group 26, claim(s) 38 and 43, drawn to a method of targeting protein for secretion from a cell, the protein comprising a sequence substantially identical to SEQ ID NO: 4.

Group 27, claim(s) 38 and 43, drawn to a method of targeting protein for secretion from a cell, the protein comprising a sequence substantially identical to SEQ ID NO: 6.

Group 28, claim(s) 50 and 55, drawn to a method of targeting protein for secretion from a cell, the protein comprising a sequence substantially identical to SEQ ID NO: 8.

Group 29, claim(s) 39-41, 43 and 44-46, drawn to a method of immunomodulating a response in an animal, the protein comprising a sequence substantially identical to SEQ ID NO: 1.

Group 30, claim(s) 39-41, 43 and 44-46, drawn to a method of immunomodulating a response in an animal, the protein comprising a sequence substantially identical to SEQ ID NO: 2.

Group 31, claim(s) 39-41, 43 and 44-46, drawn to a method of immunomodulating a response in an animal, the protein comprising a sequence substantially identical to SEQ ID NO: 4.

Group 32, claim(s) 39-41, 43 and 44-46, drawn to a method of immunomodulating a response in an animal, the protein comprising a sequence substantially identical to SEQ ID NO: 6.

Group 33, claim(s) 51-53 and 55-58, drawn to a method of immunomodulating a response in an animal, the protein comprising a sequence substantially identical to SEQ ID NO: 8.

1. This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:
The inventions listed as Groups 1-10 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-10 appears to be the polypeptide of a *Yatapoxvirus*. Fenger et al. (Journal of Virology 1976) identify the proteins associated with Yaba Monky tumor virus, a *Yatapoxvirus* (see figure 4 and 5). Therefore, the technical feature linking the inventions of groups 1-10 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of group 1-5 is considered to the polypeptide of a *Yatapoxviru,* each group encompasses different sequences.

The special technical feature of group 6-8 is considered to be the polynucleotide of a *Yatapoxvirus,* each group encompasses different sequences.

The special technical feature of group 9 is considered to be a transgenic animal comprising the gene of a *Yatapoxvirus*.

The special technical feature of group 10-13 is considered to be an antibody that recognizes a *Yatapoxvirus*, each group recognizes different sequences.

The special technical feature of group 14 is considered to be a method of detecting a *Yatapoxvirus* polypeptide.

The special technical feature of group 15-17 is considered to be a method of identifying a *Yatapoxvirus* gene, each group encompasses different sequences.

The special technical feature of group 18 is considered to be a method of identifying an immunomodulator of *Yatapoxvirus*.

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US01/32136

The special technical feature of group 19-23 is considered to be a method of identifying a *Yatapoxvirus* polynucleotide that modulates the expression of a gene, each group encompasses different sequences.

The special technical feature of group 24-28 is considered to be a method of targeting the secretion of a protein from a cell using a *Yatapoxvirus* gene sequence, each group encompasses different sequences.

The special technical feature of group 29-33 is considered to be a method of immunomodulating an immune response in an animal with *Yatapoxvirus* polypeptide, each group encompasses different sequences.

Accordingly, groups 1-33 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MA 02110-2214

PCT

WRITTEN OPINION

(PCT Rule 66)

		Date of Mailing *(day/month/year)*
Applicant's or agent's file reference 50082/015WO2		REPLY DUE within 2 months/days from the above date of mailing
International application No. PCT/US01/32136	International filing date *(day/month/year)* 11 October 2001 (11.10.2001)	Priority date *(day/month/year)* 11 October 2000 (11.10.2000)
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 39/275 and US Cl.: 424/232.1		
Applicant VIRION THERAPEUTICS INC.		

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11 February 2003 (11.02.2003).

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D. Telephone No. 703-308-0196

Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International application No.
PCT/US01/32136

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I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-49, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 50-59, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-9, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International application No.
PCT/US01/32136

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-41, 44-58

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 11-41, 44-58.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

WRITTEN OPINION

International application No.
PCT/US01/32136

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	9,10,42 and 43	YES
	Claims	1-8	NO
Inventive Step (IS)	Claims	9,10 and 43	YES
	Claims	1-8 and 42	NO
Industrial Applicability (IA)	Claims	1-10, 42, 43	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 3-8 lack novelty under PCT Article 33(2) as being anticipated by Essani et al. (Microbial Pathogenesis, 1994) . The instant invention is drawn to an immunomodulatory polypeptide derived from a Tanapox virus. The protein encodes a signal sequence and is an immunomodulatory polypeptide. Essani et al. disclose the isolation of a 38 kDa glycoprotein that is secreted from Tanapox virus infected cells which binds human interferon-gamma, human interleukin 2 and human interleukin 5 (see abstract). The reference discloses that only one protein is secreted from the Tanapox virus infected cells. Therefore, the instant invention is anticipated by Essani et al.

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by Olsen et al. (Journal of Virology, 1970). The instant invention is drawn to an immunomodulatory polypeptide derived from a Yaba poxvirus. Olsen et al. disclose the purification and acryl amide gel electrophoresis of a Yaba virion fractions (see figure 1 and discussion 1st paragraph). Any protein will be immunomodulatory when injected into an animal as it will raise an immune response. Therefore, the instant invention is anticipated by Olsen et al.

Claim 42 lacks an inventive step under PCT Article 33(3) as being obvious over by Essani et al. (Microbial Pathogenesis, 1994) in view of Paulose et al. (Microbial Pathogenisis, 1998). The instant invention is drawn to an immunomodulatory polypeptide derived from a Tanapox virus. The protein encodes a signal sequence and is an immunomodulatory polypeptide. The protein is administered as a pharmacological agent.

Essani et al. teach the isolation of a 38 kDa glycoprotein that is secreted from Tanapox virus infected cells which binds human interferon-gamma, human interleukin 2 and human interleukin 5 (see abstract). The reference discloses that only one protein is secreted from the Tanapox virus infected cells.

Paulose et al. teach the that the 38 kda protein secreted from the Tanapox virus infected cells, the references indicates that 30 N-terminal amino acids have been sequenced. The sequence has not been disclosed in the instant reference. The reference teaches that the 38 kDa protein binds TNF-alpha an inhibits the NF-kB regulated CAM pathway.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to formulate the 38 kDa protein into a pharmaceutical which can be used for the inhibition of inflammatory responses in which recruitment of leukocytes are involved. Therefore the instant invention is obvious over by Essani et al. in view of Paulose et al.

Claims 9, 10 and 43 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a composition that consists of SEQ ID NO: 1. Therefore, the invention as it relates to SEQ ID NO:1 is novel.

Claims 1-10 and 42, 43 have industrial applicability as defined by PCT Article 33(4).

---------- NEW CITATIONS ----------

WRITTEN OPINION

International application No.
PCT/US01/32136

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1, 9 and 43 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim1, 9 and 43 indefinite for the following reason(s): The claims use modifies such as "substantially identical" or "substantially pure" these terms are indefinite as the artisan would not know the metes and bounds the claimed invention. It would be impossible for the ordinary artisan to determine when a compound may be infringing because the claims as written lack definite measurable boundaries

WRITTEN OPINION

International application No.
PCT/US01/32136

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.